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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/625,854	07/23/2003	Andre Delacourte	11362.0039.NPUS01	9442

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EXAMINER	
WANG, CHANG YU	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 08/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/625,854	DELACOURTE ET AL.	
	Examiner	Art Unit	
	Chang-Yu Wang	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26,29-37,39-43 and 55-63* is/are pending in the application.

4a) Of the above claim(s) *31-37and 43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26,29,30,39-42 and 55-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *Jul 23, 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

RESPONSE TO AMENDMENT

Status of Application/Amendments/claims

Applicant's amendment filed May 26, 2006 is acknowledged. Claims 1-25, 27, 28, 38, 44-54 are cancelled. Claims 26, 29, 30-37, 39-43 and newly added claims 55-63 are pending in this application. Claims 31-37, 43 are withdrawn. It is noted that Applicant has erroneously included cancelled claim 38 as pending in the p.8 of the Remarks. Claims 26, 29, 30, 39-42 and new claims 55-63 are under examination in light of a method for aiding in the determination of whether a mammal is susceptible to or at risk of a disease associated with β-amyloid formation/aggregation. The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see p.60, line 8). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Rejections/Objections Withdrawn

The objection to claims 31-36 and 43 as encompassing non-elected subject matter is moot because the claims are withdrawn from consideration.

The rejection of claims 26, 29, 31-36, 40-43 under 35 U.S.C. 112, second paragraph, as being incomplete for omitting the controls is withdrawn in response to Applicant's amendment to the claims.

The rejection of claims 31-37 and 43 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is moot because the claims are withdrawn from consideration.

Claim Rejections/Objections Maintained

The rejection of claims 26, 29, 30, 39-42 under 35 U.S.C. 112, first paragraph as failing to comply with the enablement requirement is maintained for reasons of record in the previous office action. The rejection is applied to newly added claims 55-59 and 61-63.

Applicant argues that the instant invention provides an aid to determine the stage of AD. Applicant submits Appendix 1 of AD stages and Appendix 2 of Casas et al. Am J. Pathol. 2004. 165: 1289-1300 to support the argument. Applicant argues that the specification provides several means to detect N-terminal truncated/post-translationally modified Aβ variants and establishes a correlation between the N-terminal truncated/post-translationally modified Aβ variants and the stage of AD; thus physicians can screen patients to identify whether patients are susceptible to the disease. Applicant also argues that the 2-D electrophoresis, mass spec and in vivo animal method can be used to screen Aβ variants and detecting with specific antibodies. Applicant argues that the clearance of Aβ or predict the level of Aβ burden can be done

by measuring the amount of Aβ after administration of a known Aβ variant as recited in claim 55. Applicant further argues that any N-terminal truncated Aβ and any level of N-terminal truncated Aβ can be an indication of risk for amyloid formation/aggregation. Applicant points out that Example 1 shows that different Aβ variants are detectable in AD brains and Example 3 shows that Aβ5-42 and Aβ8-42 are identified in CSF in AD. Applicant further argues that specification provides a complete list of all possible N-terminal truncated Aβ forms and Appendix 1 shows a successful detection of Aβ1-42 to Aβ11-42. Applicant argues that the specification and Appendix1 and 2 demonstrate that the presence of N-terminal truncated species of Aβ may be considered as a factor in forecasting the onset of disease associated with amyloid formation/aggregation and the level of truncated Aβ variants can provide a clue to help determine the cause of undiagnosed symptoms even they can not be used to predict whether a patient will develop a related disease. Applicant further argues that total pool of Aβ can be determined by 2-D electrophoresis and mass spec and detected with variant specific antibodies. Applicant argues that the reduction of a total pool of Aβ after administration of a particular type of exogenous Aβ variant can determine the contribution of the administered Aβ to the total measurement and the method negates the influence of exogenous Aβ. Applicant argues that Aβ5-42, 6-42, 8-42, and 9-42 are immunogenic and the reduction of any antibodies specific for N-terminal truncated Aβ is a significant sign for the possible onset or progression of Aβ-related disease.

Applicant argues that the instant invention provides an aid to determine the stage of AD because the data shown in Appendices 1 and 2 indicate that the invention is enabling and the detecting methods provided by the specification can be used to determine whether a person is susceptible to or at risk of developing a disease related to amyloid formation/aggregation. Applicant's arguments have been fully considered but they are not persuasive. Applicant is enabled for detecting N-terminal truncated Aβ5-42 or Aβ2-42 in AD patients as shown in the literature (Wiltfang et al. J. Biol. Chem. 2001. 276: 42645-42657); however, Applicant fails to provide enough guidance as to enable one of skill in the art to detect any N-terminal truncated/post-translationally modified β amyloid variants and use them as an aid to determine whether a mammal is susceptible to any disease associated with b-amyloid formation/aggregation as recited in the claims. Although Applicant is able to detect all different forms of Aβ with N-terminal truncations, Applicant has only shown that Aβ8-42 and Aβ 5-42 are relevant to AD. The data shown in figures 4 and 7 and table 8 indicate that N-terminally truncated Aβ peptides 8-42 and 5-42 are detected in the CSF of AD patients. However, Aβ8-42 is also detected in the S0 control and so are Aβ11-42 and Aβ10-42, indicating that the presence of these forms of N-terminal truncated Aβ is a natural phenomenon. Based on the disclosure, Applicant is enabled for detecting Aβ5-42 or Aβ2-42 in AD as shown in the literature. However, Applicant is not enabled for using the detection of any form of N-terminal truncated Aβ variants as an indicator to aid in determination of which person susceptible to any amyloid-related disease because the data shown in the specification are derived from patients suffering from Alzheimer's disease rather than patients who are free of

Alzheimer's disease and later develop Alzheimer's disease. Accordingly, Applicant is also not enabled for using the detection of an increase of an antibody to any forms N-terminal truncated Aβ variants as an indicator to determine whether a person is at risk of developing any amyloid-related disease.

Applicant argues that the clearance of Aβ or predict the level of Aβ burden can be done by measuring the amount of Aβ after administration of a known Aβ variant Applicant further argues that any N-terminal truncated Aβ and any level of N-terminal truncated Aβ can be an indication of risk for amyloid formation/aggregation. Applicant's arguments have been fully considered but they are not persuasive because the data are not from patients who are free of Alzheimer's disease and later develop Alzheimer's disease. In addition, Applicant has not taught how N-terminal truncated Aβ/post-translationally modified Aβ variants are related to the clearance of Aβ or Aβ burden in a mammal. The specification has not taught what would be different in normal people and people at risk for AD in what level of Aβ and what specific Aβ variants since the clearance of Aβ occurs naturally in any persons with any conditions. The specification has not taught what level of Aβ and what type of Aβ variants are considered as an Aβ burden and what level of Aβ and what type of N-terminal truncated Aβ variants can be considered as free of an Aβ burden. Although Applicant illustrates that the reduction of total amount of Aβ after administration of a particular type of N-terminal truncated Aβ variant can be measured the clearance of Aβ, Applicant fails to demonstrate that the invention can really ignore the influence of the level of a particular type exogenous Aβ

variant and what specific type of Aβ variant. As shown in the animal model in the specification, the exogenous Aβ variant that can be distinguished is due to the species difference. However, the instant invention is drawn to a method of detecting any subject including human. Applicant fails to demonstrate that the exogenous Aβ variants have no influence in the claimed method. Since the identification of a specific Aβ variant is a key indicator to aid to determine whether a person is susceptible to a disease related to amyloid formation/aggregation, the presence and the level of that specific Aβ variant play an important role for making the decision.

Applicant argues that Aβ5-42, 6-42, 8-42, and 9-42 are immunogenic and the reduction of any antibodies specific for N-terminal truncated Aβ is a significant sign for the possible onset or progression of Aβ-related disease. Applicant's arguments have been fully considered but they are not persuasive. The administration of Aβ has been shown to cause meningoencephalitis as evidenced by the clinical trial of Aβ1-42 (AN1792) in AD patients (Mosonego et al. Science 2003. 302: 834-838). Applicant fails to demonstrate that administration of exogenous Aβ variants to a patient can avoid the adverse effect caused by these Aβ variants. Furthermore, most AD patients develop anti-Aβ autoantibodies, these anti-Aβ autoantibodies have not been well characterized. It has been speculated that these autoantibodies may help clear Aβ in normal persons (Tanzi et al. Neuron 2004. 43: 605-608). Thus, the presence of anti-Aβ could be no difference between different patients since it has also been shown that the presence or the level of anti-Aβ antibodies has no correlation with dementia (Hyman et al. Ann

Neurol. 2001. 49:808-10). Applicant fails to teach how much increased amount of antibody or reactive T-cells specific for N-terminal truncated Aβ in a mammal can be considered as at risk to develop a disease associated with Aβ-formation/aggregation. As discussed above, the instant invention is not enabling without undue experimentation commensurate in scope with the claims. Thus, the rejection of claims 26, 29, 30, 39-42 under 35 U.S.C. 112, first paragraph as failing to comply with the enablement requirement is maintained. The rejection is applied to new claims 55-63.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29, 39, 40, 55, 60 and 63 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The claims as amended are directed to a method for aiding in the determination of whether a mammal is susceptible to or at risk of a disease associated with β-amyloid formation/aggregation comprising determining the amount of one or more N-terminal truncated/post-translationally modified β-amyloid variant(s) and comparing the amount

of a particular N-terminal truncated/post-translationally modified β-amyloid from a test sample with the control samples. The instant claims now recite limitations of one or more/one or more particular N-terminal truncated/post-translationally modified β-amyloid variant, which were not clearly disclosed in the specification and claims as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in the present claims, which did not appear in the specification or original claims, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant fails to teach one or more N-terminal truncated/post-translationally modified β-amyloid as recited in claims 29 and 63. Applicant also fails to teach one or more particular N-terminal truncated/post-translationally modified β-amyloid variants as recited in claims 29, 30, 55. Applicant only describes an N-terminal truncated/post-translationally modified β-amyloid variant in the specification (see p. 12 and p. 47). The specification fails to disclose the limitation of one or more/one or more particular N-terminal truncated/post-translationally modified β-amyloid. Applicant provides no guidance as to what is encompassed within one or more particular N-terminal truncated/post-translationally modified Aβ variants. Accordingly, in the absence of sufficient recitation of one or more/one or more particular N-terminal truncated/post-translationally modified β-amyloid, the specification does not provide adequate written description to support one or more/one or more particular N-terminal truncated/post-translationally modified as recited in claim 1. Support is not found for one or more/one or more particular N-terminal truncated/post-translationally modified as disclosed in the

original specification and thus the recitations constitute new matter absent evidence for their support. Applicant is required to cancel the new matter in the reply to this office action. Alternatively, Applicant is invited to clearly point out the written support for the instant limitations.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 26, 29, 30-42, 55-63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 26, 29, 30-42, 55-63 are indefinite because the claims recite "particular". Applicant fails to define the criteria for "one or more particular N-terminal truncated/post-translationally modified β-amyloid" or "a particular disease", a skill artisan cannot determine what specific N-terminal truncated/post-translationally modified β-amyloid to be detected and what specific disease to be evaluated in order to practice the claimed invention. Thus, the claims are indefinite.

Conclusion

NO CLAIM IS ALLOWED.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang, Ph.D. whose telephone number is (571) 272-4521. The examiner can normally be reached on Monday-Friday from 8:30

AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D., can be reached at (571) 272-0867.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CYW
August 1, 2006

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER